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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 12 MAR 2004

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Applicant's or agent's file reference JAB1690f-PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/EP 03/03245	International filing date (day/month/year) 27.03.2003	Priority date (day/month/year) 02.04.2002
International Patent Classification (IPC) or both national classification and IPC C07D498/04		
Applicant JANSSEN PHARMACEUTICA N.V. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 04.09.2003	Date of completion of this report 12.03.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Allard, M Telephone No. +31 70 340-2002 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 03/03245**

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-56 as originally filed

Claims, Numbers

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
 - ☐ the language of publication of the international application (under Rule 48.3(b)).
 - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority in written form.
 - ☐ furnished subsequently to this Authority in computer readable form.
 - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
 - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
 - ☐ the claims, Nos.:
 - ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 8 (in full), 10, 11, 14, 15, 17 (all in part), 16

because:

- ☒ the said international application, or the said claims Nos. 16 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 8 (in full), 10, 11, 14, 15, 17 (all in part)
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the Standard.
- ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-14, 16-18
	No: Claims	15
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-7, 9-18
Industrial applicability (IA)	Yes: Claims	1-7, 9-15, 17, 18
	No: Claims	-

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
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International application No. PCT/EP03/03245

Reference is made to the following documents:

- D1: WO 97 25317 A (HOECHST MARION ROUSSEL, INC.) 17 July 1997 (1997-07-17)
D2: EP-A-0 885 883 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 23 December 1998 (1998-12-23)
D3: O'NEIL M J, SENIOR EDITOR: 'The Merck Index, thirteenth edition' 2001 , MERCK & CO., INC. , WHITEHOUSE STATION, NJ, US XP002246908

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claim 16 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Claim 8 in the whole has not been subject-matter of an international search.

With regard to claims 10, 11, 14, 15 and 17, the international preliminary examination is limited to those parts of said claims which have been subject-matter of a complete international search, i.e. to those parts not referring to claim 8.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Novelty (Article 33(2) PCT)

In the light of the disclosure of D3 it appears that no new technical feature is recited in claim 15, which lacks therefore novelty.

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The subject-matter of claims 1-14 and 16-18 is not disclosed in the available prior art and is therefore novel.

Inventive step (Article 33(3) PCT)

The subject-matter of claim 15, which lacks novelty, lacks necessarily an inventive step.

The subject-matter of claims 1-7, 9-14 and 16-18 lacks also an inventive step for the following reasons:

D1, which is considered to represent the closest prior art, describes hydronaphth[1,2-c]isoxazoles useful in the treatment of amongst others anxiety through serotonin antagonism. These compounds may be substituted in position 3 by a cyclic amino group.

In the light of the teachings of D1, the problem underlying and solved by the present application can be seen in the provision of further hydronaphth[1,2-c]isoxazole derivatives with the same biological activity.

To solve this problem, the present application proposes inter alia to insert between the cyclic amino group and the naphthisoxazole moiety of the compounds disclosed in D1 an alkylene linker $-(CH_2)_m-$.

D3 discloses structurally similar condensed isoxazoles, wherein a cyclic amino residue is linked to the condensed isoxazole through an alkylene linker, see examples 97, 98 and 105. These compounds are useful as antipsychotic drugs through serotonin receptor binding, see page 3, first paragraph, and page 119, experimental example 3.

In view of the teachings of D3, the introduction of the alkylene linker as proposed in the present application would appear to the skilled artisan as an obvious measure in the design of further serotonin receptor ligands.

Industrial applicability (Article 33(4) PCT)

The compounds, compositions and processes of claims 1-7, 9-15, 17 and 18 can be applied in the pharmaceutical industry.